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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,784	12/08/2005	Mitsuko Kosaka	64603(70904)	8189

21874 7590 01/08/2009

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
01/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,784	KOSAKA, MITSUKO	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/06;7/26/06;2/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 27 October 2008 has been entered in full.

Election/Restrictions

2 Applicant's election without traverse of Group III, represented by claims 7-10, drawn to a method for producing retinal nerve cells by isolating and differentiating iris pigmented epithelial cells in a serum free culture medium, in the reply filed on 27 October 2008 is acknowledged.

3. Claims 1-6, 11-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 27 October 2008.

4. Claims 7-10, are under consideration in the instant application.

Priority

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 11 June 2003. It is noted, however, that applicant has not filed a certified copy of the 166646/2003 application as required by 35 U.S.C. 119(b).

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: METHOD FOR PRODUCING RETINAL NEUROCYTE FROM NEURAL STEM CELL DERIVED FROM IRIS TISSUE.

Claim Objections

7. Claims 8-10 are objected to because of the following informalities:

Claim 10 has a typo "claims 7" instead of “claim 7”.

Claims 8-10 have “Claim” on line 1 that should begin with small case "c".

Regarding claim 9, acronyms “FGF2”, “FGF9” and “CNTF” recited should be spelled out for clarity.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing retinal nerve cells comprising isolation of iris pigmented epithelial cells (IPE) and performing adherent culturing of the IPE with DMEM/F12 or EMEM, comprising FGF2, FGF9 or CNTF for

differentiation of IPE to retinal nerve cells, does not reasonably provide enablement for a method for inducing differentiation of IPE to retinal nerve cells with any serum-free culture medium. The specification is not enabled as broadly claimed, because the culture medium and other essential factors required for inducing directed differentiation of IPE to retinal cells is not recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. The claims are drawn to a method for producing retinal nerve cells by isolating and differentiating iris pigmented epithelial cells derived from a bird or a mammal, wherein the differentiation is induced by adherent culturing in a serum-free culture medium containing one of FGF2, FGF9 and CNTF at a concentration of 1-100 ng/ml (claims 7-9). The claims also recite that the density of iris pigmented epithelial cells in the medium at the start of the adherent culture is 1×10^5 cells/cm^2 or less (claim 10).

10. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands,* 8 USPQ2d, 1400 (CAFC 1988).

11. The specification of the instant application teaches that the iris pigmented epithelial (IPE) cells, similar to retinal pigmented epithelial cells and ciliary epithelial cells, are derived from the neural plates (page 4, para 2). The specification also teaches

that the IPE cells can be isolated from an eyeball and further subjected to adherent culturing in a serum-free culture medium for inducing differentiation to retinal nerve cells (page 9, para 2), wherein the adherent culturing corresponds to a monolayer culturing step as shown in step S13 of Figure 3. Additionally, the specification states that step S13 can be performed using any "publicly known conventional culture medium" "which makes it possible to induce differentiation of iris-pigmented-epithelial-cell-derived neural stem/progenitor cells into neural cells", for example DMEM/F12, DMEM, EMEM, etc. (page 29, para 2-3). Example 1 of the instant specification demonstrates the induction of differentiation of IPE cells into retinal nerve cells by culturing in serum free DMEM/F12 culture medium with N2 supplement and growth factor FGF2 at 20ng/ml (page 39, para 5). However, the specification does not teach any methods or working examples to indicate that all possible serum-free culture medium can be used for the induction of differentiation of IPE to retinal nerve cells. Undue experimentation would be required of a skilled artisan to determine the specific medium that will have the required constituents in the required concentration for obtaining the claimed directed differentiation of IPE cells to retinal nerve cells.

12. It is well-known in the art that endogenous and exogenous factors govern the expansion, maintenance and differentiation of stem cells in vitro, a prime one being the cultivation condition. For example, Mokry et al teach that in case of adherent cultures of neural stem cells, various factors affect cell differentiation and the ratio of the resulting cell types. Modifications in culture conditions influencing cell differentiation include medium constituents like serum, growth factors, hormones, differentiation factors, etc.

Mokry et al provide a cautionary note stating that "a change in cultivation condition resulted in cell death that reduced the numbers of cells that differentiated" (Acta Med 50: 35-41, 2007; page 39, para 2). However, the relevant literature, does not teach that iris pigment epithelial cells can be induced to differentiate into retinal nerve cells by culturing the IPE cells with any serum-free culture medium as broadly claimed. The skilled artisan will not be able to make and use the claimed invention, thereby entail undue experimentation.

Please note that this rejection can be overcome by reciting the specific medium and other essential constituents required for performing the claimed method of inducing differentiaion of IPE to retinal nerve cells in the independent claim.

13. Due to the large quantity of experimentation necessary for inducing differentiation of IPE cells to retinal nerve cells using any serum-free culture medium and any factor at any concentration; the lack of direction/guidance presented in the specification; the complex nature of the invention; the unpredictability of reproducible differentiation of stem cells precipitated by changes in the cultivation conditions or medium constituents; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

14. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

15. The claims are drawn to a method for producing retinal nerve cells by isolating and differentiating iris pigmented epithelial cells derived from a bird or a mammal, wherein the differentiation is induced by adherent culturing in a serum-free culture medium containing one of FGF2, FGF9 and CNTF at a concentration of 1-100 ng/ml (claims 7-9). The claims also recite that the density of iris pigmented epithelial cells in the medium at the start of the adherent culture is 1×10^5 cells/cm^2 or less (claim 10).

16. The specification of the instant application teaches that the iris pigment epithelial (IPE) cells, similar to retinal pigmented epithelial cells and ciliary epithelial cells, are derived from the neural plates (page 4, para 2). The specification also teaches that the IPE cells can be isolated from an eyeball and subject to adherent culturing in a serum-free culture medium for inducing differentiation to retinal nerve cells (page 9, para 2), wherein the adherent culturing corresponds to a monolayer culturing step as shown in step S13 of Figure 3. Additionally, the specification states that step S13 can be performed using any "publicly known conventional culture medium" "which makes it possible to induce differentiation of iris-pigmented-epithelial-cell-derived neural stem/progenitor cells into neural cells", wherein the culture medium can be for example DMEM/F12, DMEM, EMEM, etc. (page 29, para 2-3). Example 1 of the instant specification demonstrates the induction of differentiation of IPE cells into retinal nerve cells by culturing in serum free DMEM/F12 culture medium (page 39, para 5). However,

the brief description in the specification of three examples of serum-free culture medium (DMEM/F12, DMEM, EMEM), does not provide adequate written description of an entire genus of serum-free culture medium that would be able to induce differentiation of IPE cells by adherent culture as broadly claimed. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of specific physiological characteristics, physical and/or chemical properties, functional features, structure/function correlation, or any combination thereof. However, in this case, the specification has not shown a relationship between the claimed genus of serum-free culture medium.

17. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

18. The skilled artisan cannot envision the entire genus of serum-free culture media, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

19. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

20. Therefore, only methods of adherent culture using DMEM/F12, DMEM or EMEM, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 7-10, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998) in view of Haruta et al., (Nat Neurosc 4: 1163-1164, 2001).

23. The claims are drawn to a method for producing retinal nerve cells by isolating and differentiating iris pigmented epithelial cells derived from a bird or a mammal, wherein the differentiation is induced by adherent culturing in a serum-free culture medium containing one of FGF2, FGF9 and CNTF at a concentration of 1-100 ng/ml (claims 7-9). The claims also recite that the density of iris pigmented epithelial cells in the medium at the start of the adherent culture is 1×10^5 cells/cm^2 or less (claim 10).

24. Kosaka et al. teach the isolation of iris pigmented epithelial cells (IPE) from chicken eyeballs in Eagle's MEM (page 246, column 1, "Preparation of cell"). Kosaka et al. further teach that the IPE cells are depigmented and seeded for transdifferentiation to lens tissue cells at a cellular density of $0.5\text{-}1 \times 10^4$ cells/cm^2 using monolayer cell culture (page 246, col 1, para 1-3). The reference also teaches that basic fibroblast growth factor (bFGF) or FGF2 in the culture medium at a concentration of 1-30 ng/ml, promote growth and differentiation of IPE cells (page 248, Figure 4).

25. Kosaka et al. do not teach differentiation of IPE to retinal nerve cells in a serum free culture medium.

26. Haruta et al. teach the plating and maintenance of iris tissue from adult rats in serum free culture medium containing bFGF or FGF2, resulting in the proliferation of cells as a monolayer (Figure 1a, page 1163, para 2). Haruta et al. also teach that the iris derived cells are positive for a retinal ganglion cell marker, neurofilament 200.

27. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of inducing differentiation of IPE cells to lens cells by adherent or monolayer culture method in medium containing serum as taught by Kosaka et al., to the monolayer culture in a serum free medium of Haruta et al., whereby the iris derived cells differentiate to retinal cells expressing neuronal antigen (i.e. inherently retinal nerve cells). The person of ordinary skill in the art would have been motivated because IPE and the neural retina have a common developmental origin, thereby giving rise to retinal neurons (Haruta et al. page 2163). Also, neurofilament being a retinal ganglion cell marker, its expression indicates retinal cell differentiation. Furthermore, a person of ordinary skill in the art would be motivated to use serum-free culture medium because serum is known to contain a mixture of various constituents including different growth factors that would induce differentiation to a non-specific mixture of cells, as opposed to a directed differentiation to retinal nerve cells using specific growth factors at specific concentration, as required by the instant claims. The person of ordinary skill in the art would have expected success because the method of adherent cell culture in serum free medium for differentiation of stem cells, was well established and accepted in the art at the time the invention was made.

28. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

29. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Pick et al. (Stem Cells 25: 2206-2214, 2007).

(Reference teaching the significance of serum free culture medium for directed differentiation)

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD

28 December 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649